PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44*bis*)

Applicant's or agent's file reference 2203444-WO0	**FOR FURTHER ACTION**	See item 4 below
International application No. PCT/US2006/037714	International filing date *(day/month/year)* 27 September 2006 (27.09.2006)	Priority date *(day/month/year)* 28 September 2005 (28.09.2005)
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237		
Applicant CYPRESS BIOSCIENCE, INC.		

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 *bis*.1(a).

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☒	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44*bis*.3(c) and 93*bis*.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44*bis* .2).

	Date of issuance of this report 01 April 2008 (01.04.2008)
The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. +41 22 338 82 70	Authorized officer Ellen Moyse e-mail: pt02.pct@wipo.int

Form PCT/IB/373 (January 2004)

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To: S. Peter Ludwig
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P.O. Box 5257
New York, New York 10150-5257

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)* 23 AUG 2007

Applicant's or agent's file reference	FOR FURTHER ACTION
2203444-WO0	See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US06/37714	27 September 2006 (27.09.2006)	28 September 2005 (28.09.2005)

International Patent Classification (IPC) or both national classification and IPC
IPC(8) - A61K31/165 (2007.01)
USPC - 514/619

Applicant Cypress Bioscience, Inc.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☒ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/US	Date of completion of this opinion	Authorized officer:
Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	29 April 2007 (29.04.2007)	Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/237 (cover sheet) (April 2005)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US06/37714

Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into _____ , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material

      ☐ a sequence listing

      ☐ table(s) related to the sequence listing

   b. format of material

      ☐ on paper

      ☐ in electronic form

   c. time of filing/furnishing

      ☐ contained in the international application as filed

      ☐ filed together with the international application in electronic form

      ☐ furnished subsequently to this Authority for the purposes of search

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US06/37714

Box No. V **Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims	1-20	YES
	Claims	none	NO
Inventive step (IS)	Claims	none	YES
	Claims	1-20	NO
Industrial applicability (IA)	Claims	1-20	YES
	Claims	none	NO

2. Citations and explanations:

Claims 1-20 lack an inventive step under PCT Article 33(3) as being obvious over US 2004/0228830 A1 to Hirsh et al. (hereinafter 'Hirsh').

As per claim 1, 2, and 3, directed to a method of providing long-term treatment of fibromyalgia syndrome, Hirsh discloses that milnacipran which is a norepinephrine (NE) and serotonin (5-HT) reuptake inhibitor (NSRI) (para [0004]) could produce a therapeutic effect over fibromyalgia syndrome patients (para [0017]) and that Patients received either milnacipran 75-100 mg/day twice daily for 8 weeks (para [0007]). It would have been obvious for a person having ordinary skills in the art to administer milnacipran, an NSRI and a dual re-uptake inhibitor (DRI), to provide a long-term treatment for fibromyalgia.

As per claim 4, directed to the method of claims 3, respectively, it is obvious for reasons set forth for claim 3, and further because Hirsh discloses that patients received either milnacipran 75-100 mg/day twice daily (para [0007]). It would have been obvious for a person having ordinary skills in the art to further specify that the milnacipran is administered in a dose between about 25 mg per day and about 400 mg per day.

As per claims 5, 6, directed to the method of claim 4, respectively, they are obvious for reasons set forth for claim 4, and further because Hirsh discloses that In a double-blind, randomized, multicenter clinical study, patients received 100 mg/day milnacipran or 200 mg/day (para [0007]). It would have been obvious for a person having ordinary skills in the art to further specify that the milnacipran is administered in a dose of about 100 mg per day or 200 mg per day.

As per claim 7, directed to the method of claim 1, it is obvious for reasons set forth for claim 1, and further because It would have required only ordinary knowledge in the art to administer DRI for at least 6 months to provide a longer-term treatment and durable effect for fibromyalgia.

As per claims 8 and 18, they are obvious for reasons set forth for claim 1, and further because Hirsh discloses that milnacipran could provide relief from pain (para [0017]) and that in one of the early clinical trials, milnacipran dosage of 200 mg/day was superior to the lower doses (para [0010]) and that the incidence of certain adverse events increases with dosage, including nausea, vomiting, sweating, hot flashes, palpitations, tremor, anxiety, dysuria, and insomnia (para [0008]). It would have been obvious for a person having ordinary skills in the art to administer about 200 mg per day of milnacipran for thetreatment of acute pain so as to get better therapeutic effect and then decrease the dose of milnacipran to about 100 mg per day when the acute pain has been treated to decrease the incidence of certain adverse events and administer about 100 mg per day of milnacipran to the patient for at least three months for the long-term treatment of fibromyalgia and its symptoms.

As per claim 9, directed to the method of claim 1, it is obvious for reasons set forth for claim 1, and further because Hirsh discloses that milnacipran can be administered adjunctively with other active compounds such as analgesics, antidepressants, antiepileptics, antihistamines, antimigraine drugs, antimuscarinics, sedatives, hypnotics, antipsychotics, bronchodilators, anti asthma drugs, cardiovascular drugs, corticosteroids, dopaminergics, electrolytes, gastro-intestinal drugs, muscle relaxants, nutritional agents, vitamins, parasympathomimetics, stimulants, anorectics and anti-narcoleptics (para [0086]).

As per claim 10, directed to the method of claim 9, it is obvious for reasons set forth for claim 9, and further because Hirsh discloses that "[s]pecific examples of compounds that can be adjunctively administered with milnacipran include, but are not limited to, amphetamine, caffeine clonidine codeine modafinil, morphine, gabapentin, propranolol, pregabalin, pramipexole, sibutramine, tizanidine, tramado1,and isomers, salts, and combinations thereof." (para [0087])

As per claim 11, it is obvious for reasons set forth for claims 1 and 8, and further because it would have been obvious for a person having ordinary skills in the art to administer a dual re-uptake inhibitor (DRI) to the patient for at least three months to provide long-term treatment of a pain symptom associated with fibromya1gia syndrome in a patient.

As per claims 12, 13, 14, 15, 16, 17, they are obvious for reasons set forth for claim 11, and, individually for claims 2, 3, 4, 5, 6, 7, respectively.

--Please See Continuation Sheet--

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US06/37714

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

Claims 12-18 are objected to because they are identical to claims 2-8, respectively.

Claim 12 was searched as being dependent on claim 11 instead of claim 1;
Claim 13 was searched as being dependent on claim 12 instead of claim 2;
Claim 14 was searched as being dependent on claim 13 instead of claim 3;
Claims 15 and 16 were searched as being dependent on claim 14 instead of claim 4;
Claim 17 was searched as being dependent on claim 11 instead of claim 1.

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of:

As per claim 19, directed to the method of claim 11, comprising adjunctively administering a second active compound, wherein the second active compound is selected from the group consisting of an antidepressant, an analgesic, a muscle relaxant, an anorectic, a stimulant, an antiepileptic drug, a beta blocker, a sedative, a hypnotic and combinations thereof, Hirsh discloses that "milnacipran can be administered adjunctively with other active compounds such as analgesics, antidepressants, antiepileptics, antihistamines, antimigraine drugs, antimuscarinics, sedatives, hypnotics, antipsychotics, bronchodilators, anti asthma drugs, cardiovascular drugs, corticosteroids, dopaminergics, electrolytes, gastro-intestinal drugs, muscle relaxants, nutritional agents, vitamins, parasympathomimetics, stimulants, anorectics and anti-narcoleptics." (para [0086])

As per claim 20, directed to the method of claim 19, wherein the second active compound is selected from the group consisting ofmodafinil, XP13512, gabapentin, pregabalin, pramipexole, 1DOPA, amphetamine, tizanidine, clonidine, tramadol, morphine, tricyclic antidepressants, codeine, cambamazepine, sibutramine, valium, trazodone, caffeine, nicergoline, bifemelane, propranolol, atenolol and combinations thereof, Hirsh discloses that "[s]pecific examples of compounds that can be adjunctively administered with milnacipran include, but are not limited to, amphetamine, caffeine clonidine codeine modafinil, morphine, gabapentin, propranolol, pregabalin, pramipexole, sibutramine, tizanidine, tramado1,and isomers, salts, and combinations thereof." (para [0087])

Claims 1-20 have industrial applicability as defined by PCT Article 33(4) because the subject matter can be made or used in industry.